

*Citation for published version:*

Radka, T, Reelfs, O, Dondi, R, Eggleston, I & Pourzand, C 2013, 'Improving the efficiency of aminolevulinate-photodynamic therapy of skin cancer by combining uva irradiation and potent iron chelating agents', *American Journal of Hematology*, vol. 88, no. 5, pp. E170-E171.

*Publication date:*  
2013

*Document Version*  
Early version, also known as pre-print

[Link to publication](#)

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## **IMPROVING THE EFFICIENCY OF AMINOLEVULINATE-PHOTODYNAMIC THERAPY OF SKIN CANCER BY COMBINING UVA IRRADIATION AND POTENT IRON CHELATING AGENTS**

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Photodynamic therapy (PDT) is widely used for the treatment of skin cancer. Mechanistically, in delta-aminolevulinic acid (ALA)-mediated PDT, the addition of ALA to cells bypasses the negative feedback control of heme biosynthesis, leading to accumulation of photosensitizing concentrations of protoporphyrin IX (PPIX). Subsequent activation of cellular PPIX with an external light source (usually red light, 550–750nm) leads to generation of reactive oxygen species, resulting in cell death. The major side effect of ALA-PDT treatment is the pain experienced by patients. Management of treatment-related pain still remains a considerable challenge in patients. Further optimization of the treatment protocol including light source, dose and duration therefore seems crucial to try and address this issue. To improve the efficiency of ALA-PDT of skin cells: (i) we changed the conventional light source to UVA (320–400 nm) that is absorbed more efficiently by PPIX and is 40-fold more potent in killing cultured skin cells than red light [1]; (ii) we combined ALA treatment with the potent iron chelators, salicylaldehyde isonicotinoyl hydrazone (SIH), pyridoxal isonicotinoyl hydrazone (PIH) or desferrioxamine (DFO) to further increase the accumulation of PPIX through the depletion of iron available for ferrochelatase-mediated bioconversion of PPIX to heme. Spontaneously immortalised HaCaT keratinocytes were pre-treated (or not) for 18h with SIH, PIH or DFO (20–100  $\mu$ M), then subjected to ALA (0.5 mM) for 2h and irradiated with low doses of UVA (5–50 kJ/m<sup>2</sup>). The quantification of intracellular PPIX was carried out by both HPLC and spectrofluorimetry after treatments of cells with ALA alone or combined with chelators. Cell death was examined 24h after UVA exposure of ALA+/-chelators-treated cells by flow cytometry using Annexin V-propidium iodide dual staining assay. Pretreatment of HaCaT cells with ALA caused a substantial increase in the intracellular levels of PPIX which in turn sensitized the cells to very low non-cytotoxic UVA doses. Pre-treatment with DFO, PIH and SIH followed by ALA treatment further enhanced the PPIX level in HaCaT cells and caused an additional level of photosensitization to low UVA doses. Among the chelators used, SIH combined with ALA provided the most efficient increase in PPIX and cell killing following UVA irradiation, even at a lower SIH concentration of 20  $\mu$ M. UVA-based ALA-PDT combined with SIH appears therefore to be a promising modality for topical PDT. The high lipophilicity of SIH which facilitates skin penetration and its potent cytotoxicity at low UVA doses should therefore allow the current modality for topical PDT to be improved, through a reduction of the time of irradiation and therefore the duration of pain experienced through the treatment.

[1] Buchczyk DP, Klotz LO, Lang K, Fritsch C, Sies H. Carcinogenesis 2001; 22:879–83.